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FILE LAST UPDATED:         13 SEP 2006      <20060913/UP>
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=> s CPT-11 or CPT11 or CPT () 11
          2966 CPT
            90 CPTS
          3003 CPT
                 (CPT OR CPTS)
        834457 11
           473 CPT-11
                 (CPT(W)11)
            22 CPT11
          2966 CPT
            90 CPTS
          3003 CPT
                 (CPT OR CPTS)
        834457 11
           473 CPT (W) 11
L1         486 CPT-11 OR CPT11 OR CPT (W) 11

=> s pretarget?
L2         641 PRETARGET?

=> s l1 and l2
L3          17 L1 AND L2
```

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=> s l3 not py>1998
        791952 PY>1998
L4           1 L3 NOT PY>1998

=> d ibib 1                                    .

L4     ANSWER 1 OF 1     PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:        1997041898 PCTFULL  ED 20020514
TITLE (ENGLISH):         TARGETED COMBINATION IMMUNOTHERAPY OF CANCER
TITLE (FRENCH):          IMMUNOTHERAPIE-CIBLE ASSOCIEE CONTRE LE CANCER
INVENTOR(S):             GRIFFITHS, Gary, L.;
                         HANSEN, Hans, J.
PATENT ASSIGNEE(S):      IMMUNOMEDICS, INC.;
                         GRIFFITHS, Gary, L.;
                         HANSEN, Hans, J.
LANGUAGE OF PUBL.:       English
DOCUMENT TYPE:           Patent
PATENT INFORMATION:
                         NUMBER              KIND     DATE
                         ---------------------------------
                         WO 9741898            A1 19971113
DESIGNATED STATES
       W:                AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE
                         ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS
                         LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG
                         SI SK TJ TM TR TT UA UG US UZ VN YU GH KE LS MW SD SZ
                         UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR
                         GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML
                         MR NE SN TD TG
APPLICATION INFO.:       WO 1997-US7395       A  19970502
PRIORITY INFO.:          US 1996-60/017,011      19960503


=> d kwic

L4     ANSWER 1 OF 1     PCTFULL   COPYRIGHT 2006 Univentio on STN

DETD  . . .  converted to the active metabolite which kills the
       tumor. Examples of such enzyme-prodrug binding partners
       are I antibody-carboxypeptidase G2 and topoisomerase-
       inhibiting prodrug CPT-11; beta-lactamase and
       cephalosporin-doxorubicin; alkaline phosphatase and
       etoposide phosphate; carboxypeptidase G2 and glutamic
       acid derivative of benzoic acid mustard; and beta-
       glucuronidase and the glucuronide.  .  .

       5,525,338, herein incorporated in its entirety by
       reference, discloses the use of secondary targeted
       antibodies within pretargeting protocols. In this
       embodiment, the use of biotin-avidin recognition is
       supplemented by antibody(3) recognition of the same or a
       different epitope on the.  .  .


=> s antibody (2W) enzyme
         77341 ANTIBODY
         76760 ANTIBODIES
         91010 ANTIBODY
                 (ANTIBODY OR ANTIBODIES)
        108842 ENZYME
         91174 ENZYMES
        128660 ENZYME
                 (ENZYME OR ENZYMES)
```

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L5        6489 ANTIBODY (2W) ENZYME

=> d his

     (FILE 'HOME' ENTERED AT 08:50:00 ON 14 SEP 2006)

     FILE 'PCTFULL' ENTERED AT 08:50:13 ON 14 SEP 2006
L1          486 S CPT-11 OR CPT11 OR CPT () 11
L2          641 S PRETARGET?
L3           17 S L1 AND L2
L4            1 S L3 NOT PY>1998
L5         6489 S ANTIBODY (2W) ENZYME

=> s l5 and l1
L6          31 L5 AND L1

=> s l6 not py>1998
        791952 PY>1998
L7            0 L6 NOT PY>1998

=> d kwic l6

L6     ANSWER 1 OF 31    PCTFULL   COPYRIGHT 2006 Univentio on STN

DETD  .  .  .  (TELCYTATM);
       acetogenins (especially bullatacin and bullatacinone); delta
       tetrahydrocannabinol (dronabinol, MARINOLO);
       beta-lapachone; lapachol; colchicines; betulinic acid; a camptothecin
       (including the synthetic analogue
       topotecan (HYCAMTINID), CPT-11 (irinotecan,
       CAMPTOSARO), acetylcamptothecin, scopolectin, and 9-
       aminocamptothecin); bryostatin; callystatin; CC-1065 (including its
       adozelesin, carzelesin and bizelesin
       synthetic analogues); podophyllotoxin; podophyllinic acid; teniposide;.
       .  .
 .  .  .
       to a cytotoxic polypeptide. Other insertional variants of the antibody
       molecule include the fusion to the N- or C-terminus of the
       antibody to an enzyme (e.g. for ADEPT) or a
       polypeptide which increases the serum half-life of the antibody.


=> s antibody (3W) enzyme
         77341 ANTIBODY
         76760 ANTIBODIES
         91010 ANTIBODY
                  (ANTIBODY OR ANTIBODIES)
        108842 ENZYME
         91174 ENZYMES
        128660 ENZYME
                  (ENZYME OR ENZYMES)
L8        8842 ANTIBODY (3W) ENZYME

=> s l8 and l1
L9          42 L8 AND L1

=> s l9 not py>1998
        791952 PY>1998
L10           0 L9 NOT PY>1998

=> s enzyme (3W) antibod?
        108842 ENZYME
         91174 ENZYMES
        128660 ENZYME
```

```
                (ENZYME OR ENZYMES)
         91058 ANTIBOD?
L11       7359 ENZYME (3W) ANTIBOD?

=> s l11 and l1
L12         31 L11 AND L1

=> s l12 not py>1999
        724392 PY>1999
L13          1 L12 NOT PY>1999

=> d kwic

L13    ANSWER 1 OF 1     PCTFULL   COPYRIGHT 2006 Univentio on STN

DETD   Structure-Based Classes
       1. Fluoropyrimidines
       2. Pyrimidine Nucleosides
       3. Purines
       4. Platinum Analogues
       5. Anthracyclines/Anthracenediones
       6. Podophyllotoxins
       7. Camptothecins
       B. Hormones and Hormonal Analogues
       9. Enzymes, Proteins and Antibodies
       10. Vinca Alkaloids
       11. Taxanes
       Mechanism-Based Classes
       1. Antihormonals
       2. Antifolates
       4
       . Antimicrotubule Agents
       4. Alkylating Agents (Classical and Non-Classical)
       5. Antimetabolites
       6. Antibiotics
       7. Topoisomerase Inhibitors
       8. Antivirals
       9. Miscellaneous Cytotoxic.  .  .
  .  .  .
       103;
       8. Hormones and Hormonal Analogues- Diethylstilbestrol,
       Tamoxifen, Toremefine, Tolmudex, Thymitaq, Flutamide,
       Bicalutamide, Finasteride, Estradiol, Trioxifene,
       Droloxifene, Medroxyprogesterone Acetate, Megesterol Acetate,
       Aminoglutethimide, Testolactone and others;
       9. Enzymes, Proteins and Antibodies- Asparaginase,
       Interleukins, Interferons, Leuprolide, Pegaspargase, and
       others;
       10. Vinca Alkaloids- Vincristine, Vinblastine,
       Vinorelbine, Vindesine;
       11. Taxanes- Paclitaxel, Docetaxel, and others.
  .  .  .
       since this discovery to
       developing water soluble camptothecin derivatives which
       remained in their active lactone form. Along these lines, the
       25
       recently approved Irinotecan (CPT-11) and Topotecan
       were
       developed. Irinotecan is a water soluble prodrug of the
       highly active, highly lipophilic derivative of CPT known as
       SN38 (10-hydroxy.  .  .


=> d his
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     (FILE 'HOME' ENTERED AT 08:50:00 ON 14 SEP 2006)

     FILE 'PCTFULL' ENTERED AT 08:50:13 ON 14 SEP 2006
L1           486 S CPT-11 OR CPT11 OR CPT () 11
L2           641 S PRETARGET?
L3            17 S L1 AND L2
L4             1 S L3 NOT PY>1998
L5          6489 S ANTIBODY (2W) ENZYME
L6            31 S L5 AND L1
L7             0 S L6 NOT PY>1998
L8          8842 S ANTIBODY (3W) ENZYME
L9            42 S L8 AND L1
L10            0 S L9 NOT PY>1998
L11         7359 S ENZYME (3W) ANTIBOD?
L12           31 S L11 AND L1
L13            1 S L12 NOT PY>1999

=> s antibod? (3W) enzyme
          91058 ANTIBOD?
         108842 ENZYME
          91174 ENZYMES
         128660 ENZYME
                (ENZYME OR ENZYMES)
L14        8855 ANTIBOD? (3W) ENZYME

=> s l14 and l1
L15          42 L14 AND L1

=> s l15 not py>1999
         724392 PY>1999
L16            1 L15 NOT PY>1999

=> d ibib kwic

L16    ANSWER 1 OF 1     PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:        1999042593 PCTFULL  ED 20020515
TITLE (ENGLISH):         COMPOSITIONS AND METHODS FOR SENSITIZING AND INHIBITING
                         GROWTH OF HUMAN TUMOR CELLS
TITLE (FRENCH):          COMPOSITIONS ET PROCEDES SERVANT A SENSIBILISER ET A
                         INHIBER LA CROISSANCE DE CELLULES CANCEREUSES HUMAINES
INVENTOR(S):             DANKS, Mary, K.;
                         POTTER, Philip, M.;
                         HOUGHTON, Peter, J.
PATENT ASSIGNEE(S):      ST. JUDE CHILDREN'S RESEARCH HOSPITAL;
                         DANKS, Mary, K.;
                         POTTER, Philip, M.;
                         HOUGHTON, Peter, J.
LANGUAGE OF PUBL.:       English
DOCUMENT TYPE:           Patent
PATENT INFORMATION:
                         NUMBER              KIND     DATE
                         ---------------------------------
                         WO 9942593            A1 19990826
DESIGNATED STATES
       W:                AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE
                         ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
                         KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT
                         RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU
                         ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ
                         TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT
                         SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.:       WO 1999-US3171       A  19990212
PRIORITY INFO.:          US 1998-60/075,258      19980219
```

DETD CPT-11 (irinotecan, 7-ethyl [4-(1-piperidino) piperidinolcarbonyloxycamptothecin) is a prodrug currently under investigation for the treatment of cancer that is converted to the active drug. . .

5 49:5077-5082). The specific enzyme responsible for activation in vivo of CPT-11 has not been identified, although serum or liver homogenates from several mammalian species have been shown to contain activities that convert CPT-11 to SN-38 (Tsuji, T. et al. 1991. J. Pharmacobiol. D_ynamics 14:341-349; Senter, P.D. et al. 1996. Cancer Res. 56:1471-1474; Satoh, T.

In fact, SN-38 can be detected in the plasma of animals and humans minutes after the administration of CPT-11 (Stewart, C.F. et al. 1997. Cancer Chemother. Pharmacol. 40:259-265; Kaneda, N. et al. 1990. Cancer Res. 50:1715-1720; Rowinsky, E.K. et al. 1994. Cancer. . .

. . . of this class of enzymes has yet to be identified. A recent biochemical analysis of 13 CEs compared their ability to metabolize CPT-11 to SN While the efficiency of conversion varied between enzymes, those isolated from rodents were the most efficient (Satoh, T. et al. 1994.. . .

. . . EMBL databases, including a rat serum and rat liver microsomal CE. Interestingly, CEs purified from human tissues demonstrated the least efficient conversion of CPT-11 to SN-38, with less than 5% of the prodrug being 5 converted to active drug (Leinweber, F.J. 1987. Drug Metab.

In addition to metabolism to SN-38, in humans CPT-11 is also metabolized to a compound known as APC (Haaz, M.C. et al.

In preclinical studies, CPT-11 administered to immune-deprived mice bearing human tumor xenografts produces complete regression of glioblastomas, rhabdomyosarcomas (RMS)j, neuroblastomas, and colon adenocarcinomas (Houghton, P.J. et al. 1995. Cancer Chemother. Pharmacol. 36:393-403; Houghton, P.J.. et al. 1993. Cancer Res. 53:2823-2829). However, maintenance of tumor regression in studies with CPT-11 appears to be dependent upon drug scheduling, suggesting that viable tumor cells survive therapy (i.e., minimal residual disease (MRD)). These studies also showed a steep dose-response relationship between dose of drug administered and induction of tumor regression. For example, 20 mg of CPT-11 /kg/day given daily for 5 days for two weeks produced complete regressions of Rh18 RMS xenografts, while 10 mg/kg/day given on the same schedule. . .

Similar effects were seen when mice bearing SJGC3A colon adenocarcinoma xenografts were treated with 40 mg CPT-11/kg compared to a 20 mg/kg dose.

Early clinical trials with CPT-11 indicate that the prodrug also has anti-tumor activity in vivo against many different types of solid tumors in humans. However, myelosuppression and secretory. . .

. . .

present invention, polynucleotides encoding a carboxylesterase enzyme or active fragments thereof and polypeptides encoded thereby which are capable of metabolizing the chemotherapeutic prodrug CPT-11 and its inactive metabolite APC to active drug SN-38 are disclosed. Use of this enzyme in combination with APC renders this inactive metabolite. . . invention and a disease-specific responsive promoter can be delivered to selected tumor cells to sensitize the tumor cells to the chemotherapeutic prodrug CPT-11

,

30 thereby inhibiting tumor cell growth.

Figure 5 is a linegraph comparing % cell survival, depicted on the Y-axis, at various concentrations of CPT-11,

30 depicted on the X-axis. Control Cos7 cells (filled squares) are approximately 350-fold more sensitive to CPT-11 than Cos7 cell transfected with CE (filled triangles).

Figure 8 provides the chemical structures of CPT-11, APC and SN

Figure 9A. 9B, and 9C are linegraphs showing the responses of mice bearing Rh3O and RhHpIRESI.bbit rhabdosarcoma xenografts to CPT-11 treatment. Each line on each graph shows the growth of an individual tumor. The tumor growth rate is depicted on the Y-axis. . .

. . .

depicts cells expressing rabbit CE (RhHpIRESabbit) not treated with CPT Figure 9B depicts cells expressing rabbit CE (RhHpIRES,abbit) and then treated with CPT-11 and shows complete tumor regression, even out to 12 weeks. Figure 9C depicts control cells (Rh3O) exposed to CPT-11 and shows initial regression but regrowth.

Figure 10 is a linegraph showing the effects of CPT-11 treatment on U373 glioblastoma xenografts expressing rabbit CE. Mice bearing xenografts were treated with CPT-11 (7.5 mg/kg for 5 days) for three treatment cycles. The tumor growth rate is depicted on the Y-axis in terms of tumor. . .

Detailed Descri-ption of the Invention

CPT-11 is a promising anti-cancer prodrug, that when given to patients, is converted to its active metabolite SN-38 by a human carboxylesterase. However,. . .

. . .

to compositions comprising a polynucleotide of the present invention which

have been found to be useful in sensitizing tumor cells to CPT-11 cytotoxicity by combination therapy of the prodrug and a CE enzyme. The present invention thus provides methods for

sensitizing tumor cells to. . .

. . .

In addition, the rabbit CE demonstrated greater than 85% homology with human alveolar macrophage CE yet the latter enzyme failed to convert CPT-11 to SN-38 in mammalian cells. This indicates that while CEs may have a broad range of substrate specificities, the efficiency with which similar. . .

. . .

the SV40 origin of replication allowing plasmid amplification in cells expressing the large T antigen, such as Cos7. The IC5. value for CPT-11 for cells expressing the CE was approximately B-80 fold, and most typically about 56 fold, less than that of the parent cell line thus indicating 35 that the enzyme has sensitized mammalian cells to CPT-11 (see Figure 5).

. . .

to sensitize the tumor cells to a chemotherapeutic prodrug. The ability of the combination of a rabbit CE of the present invention and CPT-11 to sensitize human tumor cells to CPT-11 was examined. Experiments were first performed to confirm that the metabolite produced by the activity of a CE of the present invention is. . .

. . .

to 5 units of CE that had been inactivated by heating produced no inhibition of cell growth. In contrast, reaction products of CPT-11 incubated with 1 to 5 units of active CE produced a 30-60% inhibition of cell growth. These data are consistent with the conversion of CPT-11 to SN-38 by CE in these cells.

The CE activity of extracts of the transfected cells was then determined. The IC511 values for CPT-11 in Rh3O rhabdomyosarcoma cells that had been stably transfected with a rabbit liver CE cDNA of the present invention or the pIRES vector. . . alone were also determined. Cells transfected with the CE cDNA contained approximately 60-fold more CE activity than control cells. The IC50 Of CPT-11 for Rh3OpIRES cells (no CE cDNA) was 4.33 X 10-6 M while the IC50 for the Rh3OpIRES.,bbit cells was 5.76 X 10-7. . . M. Therefore, the transfected cells were more than 8-fold more sensitive to CPT These data are consistent with an increased conversion of CPT-11 to SN-38 in 35 the cells transfected with a CE of the present invention.

. . .

CE of the present 5invention. These data confirm the unique ability of a CE of the present invention to activate the prodrug CPT-11 , as well as to activate one of its metabolites. Further, experiments in U-373 cells that express a CE of the present invention showed. . .

In vivo efficacy of the CE of the present invention to sensitize tumor cells to CPT-11 has also been demonstrated in two different types of tumor cells. Experiments conducted in

a mouse model demonstrate that a CE of. . . for
rabbit CE was maintained for at least 12 weeks. Importantly,
tumors were advanced (greater than 1 CM3 in volume) before
treatment with CPT-11 began. As depicted in Figure
9B, tumors
in mice expressing CE and treated with 2.5 mg CPT-11
/kg/day
25 for five days each week for two weeks (one cycle of therapy),
repeated every 21 days for a total of three. . . not regrow during
the 12
weeks of the study. In contrast, tumors that did not express
the CE regressed only transiently with CPT-11
treatment, with
30 regrowth occurring within one week after CPT-11
treatment
stopped (see Figure 9C).

. . .
In a second set of experiments, human U373 glioblastoma
xenografts that express rabbit liver CE were shown to be more
sensitive to CPT-11 than xenografts transfected with
a control
35 plasmid (no rabbit CE). Xenografts established from cells
- 22
transfected with the plasmid encoding rabbit. . .

Thus, these data support the use of the combination of
polynucleotide encoding a CE of the present invention and CPT-
11 to reduce the amount of CPT-11 needed
to produce inhibition
of tumor cell growth, or to sensitize the tumor cells to CPT-
11. These data also support the use of the present invention
10 to allow for decreased dosage with CPT-11 in
cancer patients,
thus reducing the likelihood of dose-limiting toxicity.

. . .
promoter. The vectors can then be injected into the site of
tumor removal along with systemic administration of a prodrug
such as CPT-11 to inhibit the recurrence of tumors
due to
residual tumor cells present after surgical resection of a
tumor.

Another method for delivering CEs to selected tumor
cells involves antibody direct enzyme prodrug
therapy (ADEPT).

. . .
a molecule such as rabbit
liver CE. Cellular internalization of the complex and release
of active CE would be achieved, leading to CPT-11
activation
that is specific for cells expressing the marker antigen.

25 Both the secreted and the endoplasmic reticulum-localized
protein can convert CPT-11 to SN-38; therefore, the
potential
exists for a bystander effect from cells expressing the
secreted enzyme. A similar bystander effect has been
demonstrated. . .

Extracellular activation of CPT-11 may result in
more
efficient eradication of MRD in that uninfected neighboring
tumor cells would be killed by exogenously produced SN
35 Gene therapy protocols with a secreted CE in combination with

CPT-11 may therefore be more appropriate for the elimination
of residual tumor tissue. Accordingly, in this embodiment,
- 24 -
it may be preferred. . .
. . .
the plasma. Attachment of a CE of the present
invention to the cell surface should result in local
15 extracellular activation of CPT-11 to SN-38 and
enhance local
cell kill. Purging bone marrow of contaminating tumor cells
will be accomplished by an intracellular enzyme, whereas
eradication of MRD is better achieved by an enzyme that
activates CPT-11 at an extracellular location.

CEs of the present invention cleave the COOC bond
present as an ester linkage in CPT-11 to generate
SN-38 (see
Figure 8). Since this enzyme may also catalyze the activation
of other compounds that contain such a linkage,. . .

EXAMPLES
Example 1: Identification of CEs
A CE enzyme suitable for converting CPT-11 to the
active
form, SN-38 was identified by testing a variety of samples.
. . .
CEs were commercially
available, several of these were also tested for their ability
to metabolize CPT Both rabbit and pig liver CEs
metabolized CPT-11 efficiently. The commercially
available
pig CE contained several proteins. However, the major bands
were very similar in molecular weight and did not. . .
. . .
activity of rabbit CE
The in vitro activity of rabbit liver CE was examined
in tumor cell lines. The growth inhibition of CPT-11
was
compared in cells with and without active rabbit CE. The
cells used were Rh3O cells (lo') that had been electroporated
with 20. . .

In the first assay, CPT-11 was pre-incubated with
rabbit
liver CE to produce SN-38 prior to exposure of the cells to
drug. specifically, 0.5 to 5 units of CE were incubated with
1 yM CPT-11 at 370C in DMEM medium for 2 hours. Each
reaction
mixture was then filter-sterilized and Rh3o cells were exposed
to drug for. . . was replaced
with drug-free medium containing serum. Enzyme that had been
inactivated by boiling for five minutes prior to incubation
with drug or CPT-11 to which no enzyme had been
added were
used as negative controls. Cells were allowed to grow for 3
cell doubling times. . .
. . .
the conversion of o-nitrophenyl acetate to
o-nitrophenol. Further, the Rh3OpIRES cells transfected with
rabbit CE were greater than 8-fold more sensitive to CPT-
11
than controls, as shown by a decrease in the IC,, values.

Therefore, Rh3O cells stably transfected with rabbit CE were more sensitive to growth inhibition by CPT-11 than cells that did not contain the cDNA for rabbit CE.

- 30 -

Example 5: Rabbit CE activates APC, a novel prodrug

In addition to efficiently converting CPT-11 to the active compound SN-38, experiments were also performed demonstrating the ability of rabbit liver CE to convert the 5inactive metabolic end product. . .

. . .

in the prevention of MRD. In this model, treatment of immune-deprived mice, i.e., SCID mice, bearing human NB-1691 xenografts with 10 mg/kg CPT-11 daily for 5 days on two consecutive weeks results in complete regression of the tumor. However, within 4-6 weeks, tumors are palpable. . .

. . .

identical fashion with Rh3O cells not transfected with the plasmid. When the tumors reached a size of approximately 1 cm', 2.5 mg CPT-11/kg/day was administered five days each week for two weeks (one cycle of therapy), repeated every 21 days for a total of three. . .

In contrast, tumors not expressing the CE regressed only transiently,, regrowing within one week after CPT-11 treatment had stopped (Figure 9C).

Cells were injected subcutaneously into the flanks of the SCID mice. When tumors reached approximately 1 CM3 in size, CPT-11 was administered daily for five days each week as described above, for three cycles, at a dose of 7.5 mg/kg/day.

. . .

implantation in this model during the 4 to week period when tumors are not present, followed by treatment with low doses of CPT-11, also demonstrates the effectiveness of the virus at preventing MRD. Typically, 5 since tumor regression is complete 3 weeks after commencing treatment with CPT-11, adenovirus/drug administration begins at week 4. In initial experiments, adenovirus is administered on Monday, Wednesday, Friday and CPT-11 is given daily on Tuesday through Saturday for two cycles. This permits determination of the most tolerated, effective schedule and dosage of adenovirus and CPT-11 administration to produce the longest delay of recurrent disease. These results are used to determine correct dosage for treatment of human MRD.. . .

. . .

bone marrow of these same animals contains neuroblastoma cells. The success of ex vivo purging of bone marrow with the rabbit liver CE/CPT-11 combination is demonstrated by transplanting purged bone marrow into lethally irradiated mice. If mice remain disease free for extended periods of time, this. . .

- 33 -

Example 8: Treatment of Minimal Residual Disease (MRD) in humans
The rabbit CE in combination with CPT-11 or other prodrugs activated by 'this enzyme is used to purge bone marrow 5of residual tumor cells prior to autologous bone marrow transplants. . .

Nature Med. 3:639-645). CPT-11 is administered over the next
one to six weeks to elicit tumor selective cell kill. Doses 20 and schedules of CPT-11 are determined in clinical trials of
CPT-11 by itself and in human xenograft model systems to
produce maximal tumor effect.
. . .
majority of hematopoietic progenitor cells. Two days
- 34 -
following adenoviral transduction, cells are exposed for two hours to a range of CPT-11 concentrations, usually varying
from 50 nM to 100 pM. Two days after exposure to drug, the marrow sample is harvested and stored. . .

CLMEN 13 The method of claim 12 wherein the chemotherapeutic prodrug is selected from a group consisting of CPT-11 and APC.

15 The method of claim 14 wherein the chemotherapeutic prodrug is selected from a group consisting of CPT-11 and APC.

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	15.57	15.78

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FILE LAST UPDATED: 13 Sep 2006 (20060913/ED)

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http://www.cas.org/infopolicy.html

=> s antibod? (3W) enzyme
470877 ANTIBOD?

```
        783759 ENZYME
        454161 ENZYMES
        992426 ENZYME
                  (ENZYME OR ENZYMES)
L17       6081 ANTIBOD? (3W) ENZYME

=> s CPT-11/cn
   REG1stRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.




L19          0 L18

=> s CPT11/cn
   REG1stRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.




L21          0 L20

=> s cpt 11/cn\
'CN\' IS NOT A VALID FIELD CODE
L22          0 CPT 11/CN\

=> s cpt 11/cn
   REG1stRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.




L24        888 L23

=> d his

     (FILE 'HOME' ENTERED AT 08:50:00 ON 14 SEP 2006)

     FILE 'PCTFULL' ENTERED AT 08:50:13 ON 14 SEP 2006
L1          486 S CPT-11 OR CPT11 OR CPT () 11
L2          641 S PRETARGET?
L3           17 S L1 AND L2
L4            1 S L3 NOT PY>1998
L5         6489 S ANTIBODY (2W) ENZYME
L6           31 S L5 AND L1
L7            0 S L6 NOT PY>1998
L8         8842 S ANTIBODY (3W) ENZYME
L9           42 S L8 AND L1
L10           0 S L9 NOT PY>1998
```

```
L11        7359 S ENZYME (3W) ANTIBOD?
L12          31 S L11 AND L1
L13           1 S L12 NOT PY>1999
L14        8855 S ANTIBOD? (3W) ENZYME
L15          42 S L14 AND L1
L16           1 S L15 NOT PY>1999

     FILE 'CAPLUS' ENTERED AT 08:55:25 ON 14 SEP 2006
L17        6081 S ANTIBOD? (3W) ENZYME
                S CPT-11/CN

     FILE 'REGISTRY' ENTERED AT 08:55:50 ON 14 SEP 2006
L18           0 S CPT-11/CN

     FILE 'CAPLUS' ENTERED AT 08:55:51 ON 14 SEP 2006
L19           0 S L18
                S CPT11/CN

     FILE 'REGISTRY' ENTERED AT 08:55:58 ON 14 SEP 2006
L20           0 S CPT11/CN

     FILE 'CAPLUS' ENTERED AT 08:55:59 ON 14 SEP 2006
L21           0 S L20
L22           0 S CPT 11/CN\
                S CPT 11/CN

     FILE 'REGISTRY' ENTERED AT 08:56:12 ON 14 SEP 2006
L23           1 S CPT 11/CN

     FILE 'CAPLUS' ENTERED AT 08:56:12 ON 14 SEP 2006
L24         888 S L23

=> s l24 and l17
L25           7 L24 AND L17

=> s l17 (L) l24
L26           1 L17 (L) L24

=> d ibib

L26  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2002:236399  CAPLUS
DOCUMENT NUMBER:          136:268117
TITLE:                    Antibody-enzyme conjugates for increasing the
                          target-specific toxicity of a chemotherapy drug
INVENTOR(S):              Griffiths, Gary L.; Hansen, Hans J.
PATENT ASSIGNEE(S):       Immunomedics, Inc., USA
SOURCE:                   U.S., 8 pp.
                          CODEN: USXXAM
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   2
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
     ---------------      ----   --------    --------------------     --------
     US 6361774            B1    20020326    US 1999-399221           19990917
     US 2002114808         A1    20020822    US 2002-66782            20020206
PRIORITY APPLN. INFO.:                       US 1998-101039P      P   19980918
                                             US 1999-399221       A3  19990917
REFERENCE COUNT:          32     THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS
                                 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
```

=> d l25 ibib 1-7

L25 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:546856 CAPLUS
DOCUMENT NUMBER: 143:73869
TITLE: Design and sequences of human butyrylcholinesterase variants that alter the activity of anticancer agents and the use in cancer treatment
INVENTOR(S): Watkins, Jeffry D.; Pancook, James D.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 60 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005136044	A1	20050623	US 2003-728723	20031204
PRIORITY APPLN. INFO.:			US 2003-728723	20031204

L25 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:817401 CAPLUS
DOCUMENT NUMBER: 141:289026
TITLE: Rabbit liver carboxylesterase capable of activating chemotherapeutic prodrug and thereby sensitizing and inhibiting growth of human tumor cells
INVENTOR(S): Danks, Mary K.; Potter, Philip M.; Houghton, Peter J.
PATENT ASSIGNEE(S): St. Jude Children's Research Hospital, USA
SOURCE: U.S., 39 pp., Cont.-in-part of WO 99 42,593.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6800483	B1	20041005	US 2000-595682	20000616
WO 9942593	A1	19990826	WO 1999-US3171	19990212
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2004259829	A1	20041223	US 2004-858271	20040601
PRIORITY APPLN. INFO.:			US 1998-75258P P	19980219
			WO 1999-US3171 A2	19990212
			US 2000-595682 A1	20000616

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:453053 CAPLUS
DOCUMENT NUMBER: 141:1228
TITLE: Use of multi-specific, non-covalent complexes for targeted delivery of therapeutics
INVENTOR(S): Griffiths, Gary L.; Govindan, Serengulam V.; Hansen, Hans J.
PATENT ASSIGNEE(S): Immunomedics, Inc., USA; McCall, John Douglas

SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004045642	A1	20040603	WO 2003-GB4994	20031117
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2505717	AA	20040603	CA 2003-2505717	20031117
AU 2003283599	A1	20040615	AU 2003-283599	20031117
US 2004166115	A1	20040826	US 2003-714391	20031117
EP 1560596	A1	20050810	EP 2003-775576	20031117
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006514627	T2	20060511	JP 2004-552884	20031117

PRIORITY APPLN. INFO.: US 2002-426379P P 20021115
WO 2003-GB4994 W 20031117

L25 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:584407 CAPLUS
DOCUMENT NUMBER: 139:358244
TITLE: Carboxylesterase-mediated sensitization of human tumor cells to CPT-11 cannot override ABCG2-mediated drug resistance
AUTHOR(S): Wierdl, Monika; Wall, Amelia; Morton, Christopher L.; Sampath, Janardhan; Danks, Mary K.; Schuetz, John D.; Potter, Philip M.
CORPORATE SOURCE: Department of Molecular Pharmacology, St. Jude Children's Research Hospital, Memphis, TN, USA
SOURCE: Molecular Pharmacology (2003), 64(2), 279-288
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:236399 CAPLUS
DOCUMENT NUMBER: 136:268117
TITLE: Antibody-enzyme conjugates for increasing the target-specific toxicity of a chemotherapy drug
INVENTOR(S): Griffiths, Gary L.; Hansen, Hans J.
PATENT ASSIGNEE(S): Immunomedics, Inc., USA
SOURCE: U.S., 8 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 6361774	B1	20020326	US 1999-399221		19990917
US 2002114808	A1	20020822	US 2002-66782		20020206
PRIORITY APPLN. INFO.:			US 1998-101039P	P	19980918
			US 1999-399221	A3	19990917

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:549389 CAPLUS
DOCUMENT NUMBER: 131:165300
TITLE: Rabbit liver carboxylesterase capable of activating chemotherapeutic prodrug and thereby sensitizing and inhibiting growth of human tumor cells
INVENTOR(S): Danks, Mary K.; Potter, Philip M.; Houghton, Peter J.
PATENT ASSIGNEE(S): St. Jude Children's Research Hospital, USA
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9942593	A1	19990826	WO 1999-US3171	19990212
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2320808	AA	19990826	CA 1999-2320808	19990212
AU 9928679	A1	19990906	AU 1999-28679	19990212
AU 755251	B2	20021205		
EP 1054979	A1	20001129	EP 1999-909488	19990212
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002504340	T2	20020212	JP 2000-532533	19990212
US 6800483	B1	20041005	US 2000-595682	20000616
US 7018631	B1	20060328	US 2000-622568	20000831
US 2004259829	A1	20041223	US 2004-858271	20040601
PRIORITY APPLN. INFO.:			US 1998-75258P	A2 19980219
			WO 1999-US3171	W 19990212
			US 2000-595682	A1 20000616

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:277438 CAPLUS
DOCUMENT NUMBER: 131:97098
TITLE: Comparison of activation of CPT-11 by rabbit and human carboxylesterases for use in enzyme/prodrug therapy
AUTHOR(S): Danks, Mary K.; Morton, Christopher L.; Krull, Erik J.; Cheshire, Pamela J.; Richmond, Lois B.; Naeve, Clayton W.; Pawlik, Cynthia A.; Houghton, Peter J.; Potter, Philip M.
CORPORATE SOURCE: Department of Molecular Pharmacology [M. K. D., C. L. M., E. J. K., P. J., St. Jude Children's Research Hospital, Memphis, TN, 38105, USA

SOURCE: Clinical Cancer Research (1999), 5(4), 917-924
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	10.04	46.70

STN INTERNATIONAL LOGOFF AT 08:57:41 ON 14 SEP 2006

WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Thursday, September 14, 2006

Hide?	Set Name	Query	Hit Count
	DB=PGPB,USPT,EPAB; PLUR=YES; OP=ADJ		
☐	L57	L56 and DTPA	2
☐	L56	CPT-11 and (l49 or l48)	2
☐	L55	20020114808.pn.	1
☐	L54	L53 not @py>1997	14
☐	L53	L52 and enzyme	2731
☐	L52	L51 and l50	2737
☐	L51	bi-specific or bispecific	10297
☐	L50	pre-target$ or pretarget$	3097
☐	L49	7074405.pn.	1
☐	L48	6962702.pn.	1
☐	L47	7018631.pn.	1
☐	L46	L44 not @ay>1998	1
☐	L45	L44 not @ay>1997	0
☐	L44	L43 and l42	242
☐	L43	enzyme or esterase	258937
☐	L42	L41 and l40	242
☐	L41	CPT-11 or CPT 11	1923
☐	L40	pretargeting	2775
☐	L39	anti-DTPA	22
☐	L38	anti-DTPAA	0
☐	L37	anti-DPTA	0
☐	L36	L29 and L35	20
☐	L35	L26 not @py>1998	26
☐	L34	L33 and prodrug	42
☐	L33	L15 and L32	574
☐	L32	L31 not @py>1998	853
☐	L31	L29 and enzyme	7806
☐	L30	L29 and enzzyme	0
☐	L29	DTPA	11297
☐	L28	L27 not @py>1998	4
☐	L27	hapten and ADEPT	234

☐	L26	hapten and pretargeting	324
☐	L25	L24 not @ay>1998	2
☐	L24	L15 and L23	276
☐	L23	esterase and L22	306
☐	L22	L13 and prodrug	1333
☐	L21	6043367.pn.	1
☐	L20	L19 and L8	7
☐	L19	L18 not @ay>1998	22
☐	L18	L17 and prodrug	126
☐	L17	L16.ab.	527
☐	L16	camptothecin	5165
☐	L15	antibod$	175686
☐	L14	L13 not @ay>1998	881
☐	L13	CPT	4944
☐	L12	L11 not @ay>1999	4
☐	L11	L10 and CPT	52
☐	L10	L9 and antibod$	799
☐	L9	L8 and bispecific	800
☐	L8	glucuronid$	12716
☐	L7	L6 not @py>1998	18
☐	L6	L5 and enzyme	2168
☐	L5	L2 and prodrug	2340
☐	L4	L3 not @py>1998	0
☐	L3	L2 and pretargeting	298
☐	L2	epirubicin	4173
☐	L1	5851527.pn.	1

END OF SEARCH HISTORY